PAPER

Evaluation of the effect of colloid (Haemaccel) on the bleeding time in the trauma patient

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INTRODUCTION

Haemaccel is widely used throughout Europe and South Africa in the resuscitation of trauma patients[1]. Although it is very effective when used as the sole volume expander, it is usually used in conjunction with a crystalloid which has been shown both experimentally and clinically to increase its benefits[2]. The colloid within Haemaccel is chemically modified bovine bone gelatine preparation. The gelatine is subjected to thermal degradation to produce a gelatine hydrolysate in the form of small polypeptides of molecular weight 12 000 to 15 000. These are then cross linked to form larger molecules which have an average molecular weight of 35 000 (range 25 000–50 000). In addition, the solution contains a number of other solutes including Ca^{2+} (6.2 mM), and exerts an oncotic pressure of 3.4–3.8 kaPa at 37°C. It is isoncotic with plasma and it has a half life in the body of approximately 5 h.

Recent anecdotal reports from the Department of Surgery at the University Hospital Bloemfontein (Orange Free State, South Africa) suggested that trauma patients who had received Haemaccel for shock exhibited an increased bleeding tendency in the form of wound oozing, both intra- and post-operatively. The aim of the present study, therefore, was to perform a controlled investigation of the effects of Haemaccel on bleeding time *in vivo* in trauma victims at the Trauma Unit of Johannesburg Hospital.

PATIENTS AND METHODS

Protocol

Twenty-five patients who presented at the Trauma Unit of the Johannesburg Hospital were recruited over a 35 day period. All patients in our study had suffered either blunt or penetrating trauma, and all required fluid resuscitation due to their injuries. All patients were seen by the On call Trauma Team which consisted of a consultant, a registrar, two senior house officers and a house officer, along with the Trauma Nursing Team in the resuscitation room. The patients were scored independently by the staff of the trauma unit using the Injury Severity Score (ISS)[3,4] and Revised Trauma Score systems[5,6]. For inclusion in the study the patients had to satisfy the following series of pre-determined criteria

1 Age > 16 years
2 Blunt or penetrating trauma
3 Required intravenous fluid resuscitation
4 Arrival at trauma unit within 2 h of injury
5 Crystalloid (Ringer's lactate) as the only pre-hospital infusion
6 No underlying illness or medication which would affect the patient's coagulating system

All the patients described in this study were received in the Trauma Unit within 2 h of the injury. They were all treated according to the Advanced Trauma Life Support Programme guidelines relating to resuscitation in pre-hospital phase[7], having received only crystalloid (Ringer's lactate) as the volume expander. Base line bleeding time was determined for each patient on arrival at the hospital using the Simplate type II method as well as a full coagulation screen (see below). The patients were then allocated randomly into one of two groups to receive either (i) colloid (Haemaccel: group 1) or (ii) further crystalloid (Ringer's lactate; group 2), until the patient was fully resuscitated, the end point being stable vital signs. The volume of fluid given was documented and a further bleeding time and full coagulation screen was carried out. A list of patients included in each group, and the injuries can be obtained from the authors.

Ethical approval was obtained from the Ethics Committee of the University of the Witwatersrand.

Coagulation screen

Approximately 20 ml of blood withdrawn from a femoral vein by direct venepuncture. Initial normalized ratio (INR), prothrombin, partial thromboplastin and thrombin times were determined using a 1:10 standard dilution of sodium citrate (31.3 gl). Platelet count was determined from a separate aliquot of the venous blood collected in EDTA.

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Table 1 **Number of patients (*N*), males/females (m/f) and associated ages, suffering blunt or penetrating (pene) injuries, injury severity scores (ISS) and revised trauma scores (RTS). Following an initial resuscitation with crystalloid (Init-resusc), the patients were randomized into two groups and resuscitated further (Secondary-resusc) with either colloid (group 1) or crystalloid (group 2). All variables except *N* and injuries presented as medians (interquartile ranges).**

	Group 1 (Colloid)	*Group 2 (Crystalloid)*
N (m/f)	11 (9/2)	14 (12/2)
Age (year)	30 (29–38)	30 (25–39)
Injuries (blunt/pene)	7/4	9/5
ISS	25 (16–34)	25 (14–36)
RTS	7.5 (4.9–7.8)	6.3 (4.4–7.8)
Init-resusc crystalloid vol (Ref 3)	1.0 (0.2–1.5)	0.8 (0.4–1.0)
Secondary-resusc vol (Ref 3)	1.0 (1.0–1.8)	2.2* (2.0–2.6)

*$P<0.05$ group 1 versus group 2, Mann–Whitney *U* test

Statistical analysis

Within group comparisons were made using a Willcoxon match-paired signed rank test, while comparisons between crystalloid and colloid groups were made using a Mann–Whitney *U*-test. A value of $P<0.05$ was considered statistically significant. All values are presented as median (interquartile range) unless indicated otherwise.

Results

The patients' ages, ISS and volumes of crystalloid used for initial resuscitation in the two groups are summarized in Table 1. These values did not differ significantly between the two groups. Furthermore, bleeding times, prothrombin, thrombin, partial thromboplastin times and platelet counts did not differ significantly between the two groups at the end of the initial resuscitation.

Effects of secondary resuscitation with either crystalloid or colloid solutions

The volume of fluid used for secondary resuscitation was significantly greater in the crystalloid treated group compared to that treated with colloid (Table 1). Following secondary resuscitation there was statistically significant increase in bleeding time in both groups (Figure 1). However, the increase in bleeding time was significantly greater in the colloid than in the crystalloid treated group, amounting to an increase of 5.5 min (2.8–7.3) or 93.6% (42.3–157.1) in the colloid group compared to 1.4 min (1.0–2.3) or 25.1% (14.1–46.9) in the crystalloid treated group. Prothrombin time showed a small increase in both groups (Figure 2), which failed to attain statistical significance. The thrombin time was unchanged in either group following secondary resuscitation from 28.8 s (26.7–33.0) and 30.7 s (25.2–32.4), respectively, in groups 1 and 2. Partial thromboplastin time was increased significantly in the colloid treated group. However, the increase in the crystalloid group failed to achieve statistical significance ($P=0.068$, Figure 3). There was a decrease in platelet count in both groups (Figure 4). These changes were not statistically significant. Although there was a marked increase in bleeding time in the colloid group, there was no direct relationship between the volume of colloid given and prolongation of bleeding times. The volumes of whole blood subsequently required by the crystalloid group was less than that required by the colloid group (3.5 units; (range 0–11) versus 4.6 units; (range 0–26), respectively).

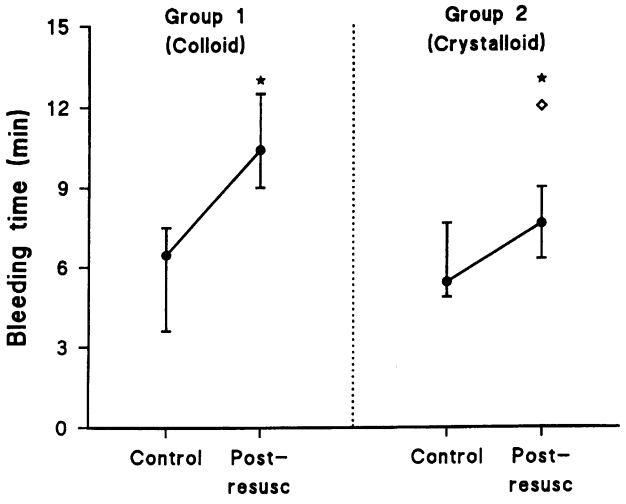

Figure 1 **Bleeding times in two groups of patients recorded after the initial resuscitation with crystalloid (control) and again after secondary resuscitation with either colloid (group 1) or crystalloid (group 2). *$P<0.05$ versus respective control, Willcoxon matched-pairs signed ranks test. $P<0.05$ versus group 1, Mann–Whitney *U*-test**

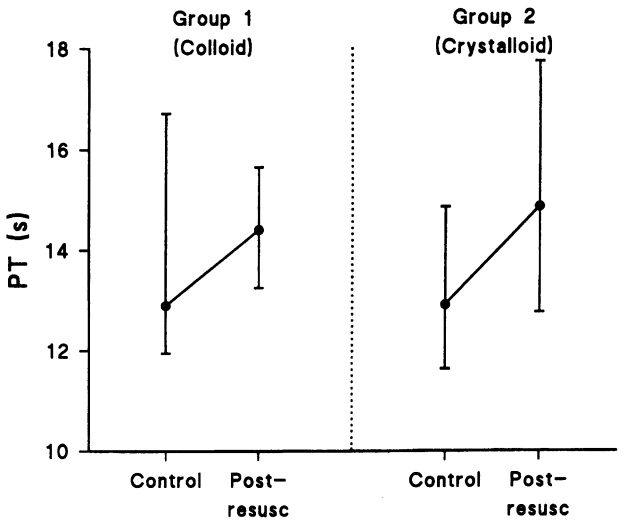

Figure 2 **Prothrombin times (PT) in two groups of patients recorded after the initial resuscitation with crystalloid (control) and again after secondary resuscitation with either colloid (group 1) or crystalloid (group 2)**

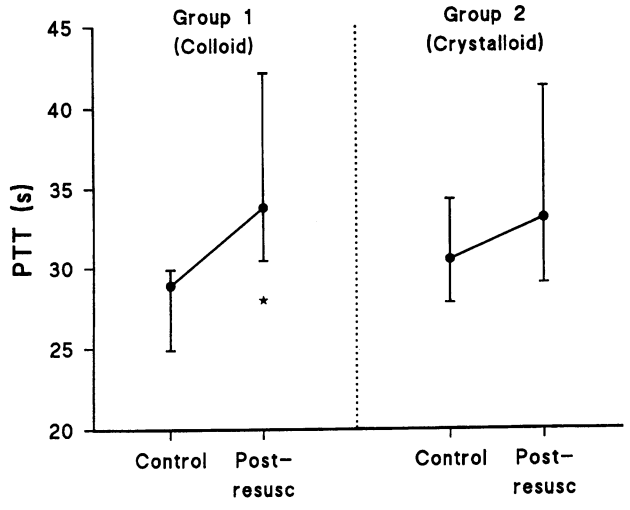

Figure 3 **Partial thromboplastin times (PTT) in two groups of patients recorded after the initial resuscitation with crystalloid (control) and again after secondary resuscitation with either colloid (group 1) or crystalloid (group 2) *$P < 0.05$ versus respective control, Willcoxon matched-pairs signed ranks test**

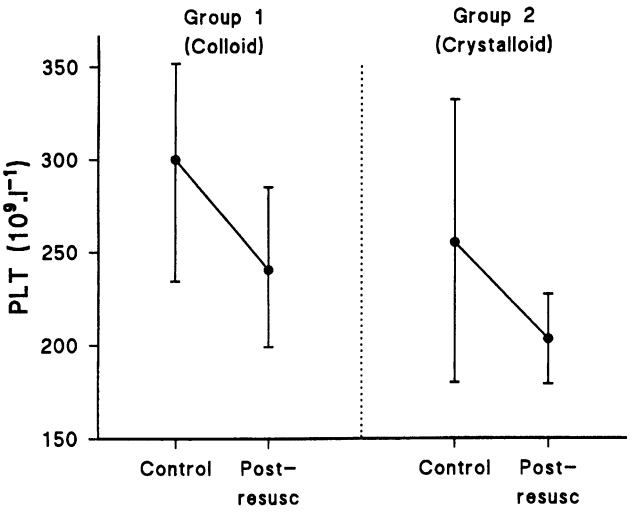

Figure 4 **Platelet counts (PLT) in two groups of patients recorded after the initial resuscitation with crystalloid (control) and again after secondary resuscitation with either colloid (group 1) or crystalloid (group 2)**

DISCUSSION

The present study has shown that there is an increase in bleeding time following resuscitation with asanguineous fluids, and that this increase is markedly greater when the fluid used is Haemaccel rather than crystalloid solution. It is difficult to assess the clinical significance of this finding; however, it was noted that the requirement for whole blood was somewhat higher in the group of patients treated with Haemaccel, when compared to those treated with crystalloid solution. While we accept that this finding may be artefactual because the discharge haemoglobins were not measured and that there were a relatively small number of patients in our study, it remains a worrying finding. Obviously, a larger study is required to validate this particular result.

There are a number of potential mechanisms which could explain the increase in the bleeding time.

Haemostasis refers to the spontaneous arrest of bleeding from an injured blood vessel. Primary haemostasis in the trauma patient is initiated by the adhesion of platelets to the site of injury and local vasoconstriction with subsequent formation of a haemostatic plug brought about initially by the aggregation of platelets on their exposure to collagen. The bleeding time is thought to be one of the few global tests of haemostatic competency and reflects both platelet function as well as number[8]. It has been recognized and used in the surgical patient as an indicator of bleeding tendencies both pre-and post-operatively[9]. The primary haemostasis is followed by secondary haemostasis in which the coagulation system is activated resulting in stabilization of the initial platelet plug by fibrin.

The prolongation of bleeding time in the present study may, thus, be due to a deficiency in the primary haemostatic mechanism. Although in our study the platelet count dropped in both groups, they did not fall below physiological levels, nor was the decline statistically significant. Thus, the increased bleeding cannot be explained simply on the basis of a reduced platelet count. White *et al.*[8] feel that the bleeding time evaluates platelet function. There is little evidence that Haemaccel may affect platelet function *in vivo* following trauma. In the rat bleeding time and blood loss were increased following liver resection and plasma replacement with Haemaccel, while ADP-induced platelet aggregation was significantly decreased after the infusion of Haemaccel[10]. Furthermore, *in vitro* studies have suggested that Haemaccel can inhibit von Willebrand factor and thereby reduce platelet aggregation[11,12], thus simulating von Willebrand's disease.

This inhibition was found to be dose dependent, and could be overcome by increasing the amount of von Willebrand factor, but was not found to prolong *in vitro* bleeding time significantly. These workers found that collagen, ADP, adrenaline induced platelet aggregation and serotonin release were inhibited markedly by Haemaccel. Thus, the increase in bleeding time following Haemaccel reported in the present study could be due to inhibition of platelet function.

Haemaccel may modify platelet function by coating of the platelet membrane with the colloid macromolecule causing a steric blockade of the surface receptors as occurs with other macromolecules[13,14] thus interfering with the binding of ADP, collagen and adrenaline, resulting in a reduction in platelet aggregation and adhesion. This has been shown to occur *in vitro* but has not been shown to be of clinical significance. Platelet function can also be modified by ionized calcium.

Heptinstalls[15] showed that free calcium ions, even at normal physiological levels, can reduce platelet aggregation *in vitro*, partly by promoting platelet disaggregation. Since Haemaccel contains free calcium ions (6.25mM), it might increase plasma calcium levels and hence reduce platelet aggregation *in vivo*.

Finally, a slight prolongation of prothrombin and partial thromboplastin times was also noted (in both groups) but these remained within the normal limits of the normal range and reflect a degree of haemodilution of the coagulation factors which occurred during volume replacement. A transient dilutional coagulopathy is consistent with earlier reports[16], though other studies suggest that this is rapidly corrected when perfusion is good[17].

In summary, the present study has shown that volume replacement with Haemaccel in the trauma patient produces a markedly greater increase in bleeding time compared to resuscitation with a crystalloid solution. Further studies are now required to elucidate the exact mechanisms of this action.

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